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CORRESPONDENCE

The scientific value of tractography: accuracy vs usefulness

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Abstract

Tractography has emerged as a central tool for mapping the cerebral white matter architecture. However, its scientific value continues to be a subject of debate, given its inherent limitations in anatomical accuracy. This concise communication showcases key points of a debate held at the 2024 Tract-Anat Retreat, addressing the trade-offs between the accuracy and utility of tractography. While tractography remains constrained by limitations related to resolution, sensitivity, and validation, its usefulness and utility in areas such as surgical planning, disorder prediction, and the elucidation of brain development are emphasized. These perspectives highlight the necessity of context-specific interpretation, anatomically informed algorithms, and the continuous refinement of tractography workflows to achieve an optimal balance between accuracy and utility.

"Le mieux est le mortel ennemi du bien".
- Montesquieu's Pensées (1726).
This quote, often misattributed to Voltaire, highlights how the pursuit of perfection can sometimes undermine what is already good.

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Opening statement

Tractography offers a glimpse into the complex network of connections that enable human cognition and behavior. Despite its promise, tractography faces a formidable challenge: the brain's incredible complexity over all scales. Limitations of diffusion magnetic resonance imaging (dMRI) tractography are inherent to the fact that dMRI is an indirect measurement of the white matter architecture and will always be limited by spatial resolution. However, does it mean that tractography cannot be useful or valuable in specific situations or at a particular scale? At the International Society of Tractography, the debate titled "Neuroanatomy is too complicated to be solved by tractography" led to discussions regarding the strengths and limitations of dMRI tractography and its role in modern neuroscience. This commentary examines the dichotomy between the accuracy and usefulness of tractography, highlighting the importance of anatomically informed tractography reconstruction (Table 1).

Proof tractography is useful

- **Neurosurgical planning**: Tractography helps surgeons identify critical white matter pathways near tumors, enabling them to plan surgical approaches that minimize

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Table 1 Summary of tractography applications and limitations across Spatial scales. This table highlights how the goals and accuracy of tractography vary across macro-, meso-, and microscale levels of brain analysis. At the **macroscale**, tractography is highly useful for clinical applications such as neurosurgical planning and targeting in deep brain stimulation (DBS) or focused ultrasound (FUS), with reliable identification of major white matter pathways. The **mesoscale** enables functional network modelling and translational insights into neuropsychiatric disorders, with moderate anatomical correspondence to invasive tracer studies. At the **microscale**, tractography contributes to developmental and structural modelling, though its accuracy is limited by the resolution constraints of diffusion MRI and indirect Estimation of axonal pathways

Goal Scale	Useful	Accurate
Macroscale	Assists in neurosurgical planning to avoid critical pathways and guides DBS and FUS for precise targeting.	Identifies major white matter pathways reliably and reproducibly.
Mesoscale	Supports predictions of network functions underlying neuropsychiatric disorders and provides a foundation for personalized therapies.	Provides reasonable correlation with tracer studies in non-human primates for connectivity patterns.
Microscale	Contributes to understanding axonal growth, brain geometry, and developmental processes.	Limited by the resolution of dMRI; indirect approximations of axonal pathways;

damage to essential brain regions (Kamagata et al. 2024; Krieg et al. 2017; Radwan et al. 2024).

- **Deep brain stimulation (DBS)**: Tractography aids in understanding the relationship between DBS electrode placement and treatment outcomes, facilitating more precise targeting of brain regions involved in movement disorders and other conditions (Alagapan et al. 2023; Calabrese 2016).
- **Focused Ultrasound (FUS)**: This was recently approved for the treatment of refractory essential tremor and similarly to DBS, more precise targeting can be achieved using tractography (Feltrin et al. 2022; Krishna et al. 2019).
- **Cognition and disorder predictions**: Tractography, when combined with complementary datasets, offers a data-driven approach to predicting neurological deficits, such as those seen in stroke or neurodegenerative conditions. This predictive capability supports the development of personalized interventions and enables targeted therapies by linking brain disconnection patterns to cognitive or clinical outcomes (Forkel et al. 2022; Gonzalez-Aquines et al. 2019; Talozzi et al. 2023; Thiebaut de Schotten & Forkel, 2022).
- **Understanding brain geometry and development**: Tractography data can contribute to a better understanding of how axons grow and connect, how brain geometry is influenced by development, and vice versa (Chenot et al. 2019; David et al. 2019; Hau et al. 2016; Maffei et al. 2019; Petit et al. 2022).

Proof tractography is accurate

- **Capable of finding major fiber tracts**: Tractography has consistently demonstrated its ability to identify white matter pathways in the brain at the macroscale. While it may not perfectly replicate the full extent of these tracts, it offers valuable insights into their overall course and location (Schilling et al. 2020). While different tractography algorithms may yield varying results, the overall process of tractography is largely reproducible and has been validated using post mortem dissection (macroscale). This means that repeated scans of the same individual are likely to produce consistent findings, providing reliability to the technique (Yeh et al. 2016).
- **Correlation with tracer studies**: While some studies noted that correspondence between tractography and tracer is inherently limited (Thomas et al. 2014), several studies have shown a modest to strong correlation between tractography results and findings from invasive tracer studies in non-human primates. The divergence in reports may stem from different studies using different tracer techniques or databases, different dMRI data, and different tractography algorithms. While imperfect, this suggests that tractography can reasonably represent connectivity patterns (Azadbakht et al. 2015; Knösche et al. 2015; Roebroeck et al. 2019; Yendiki et al. 2022). However, no complete connectome in non-human primates has been achieved.
- **Correlation with human histology studies**: Several studies have shown a modest to strong correlation between findings from histology techniques with dMRI orientation estimates (Budde and Annese 2013; Khan and Hashmi 2015; Mollink et al. 2017; Seehaus et al. 2015) and the tractography based on them. Although inferred sensitivity and specificity of tractography are imperfect (Reveley et al. 2015; Roebroeck et al. 2008; Thomas et al. 2014) this suggests that tractography can reconstruct macro- and mesoscale connectivity patterns when its validated strengths and limitations are taken into account (Roebroeck et al. 2019; Yendiki et al. 2022), as discussed below. Furthermore, its accuracy could be further improved when jointly modeled with microscopy in ex vivo situations (Howard et al. 2019).

Tractography is not perfect, but we know its limitations

While different tractography algorithms may yield varying results, the overall tractography process is largely reproducible. This means that repeated scans of the same individual are likely to produce consistent findings, demonstrating a degree of reliability.

- **Sensitivity/Specificity Trade-off**: High sensitivity (detecting all true connections) often comes at the cost of reduced specificity (avoiding false connections) and vice versa. This means that researchers and clinicians must carefully consider the trade-offs and choose tractography parameters that align with their specific objectives (Bastiani et al. 2012; Maier-Hein et al. 2017; Schilling et al. 2019; Seehaus et al. 2013; Thomas et al. 2014).
- **Limited resolution and indirect nature**: The resolution of diffusion MRI data is significantly lower (millimeter scale, typically ranging from 1.5 mm to 2.5 mm) than the microscopic scale of individual axons (micrometer scale. The average axon diameter, excluding the myelin sheath, is typically 1 to 10 micrometers). On top of limited resolution, dMRI only offers indirect measurements for local structures, since its signal emerges from diffusion of water molecules. Consequently, local models, upon which tractography is based, can deviate significantly from accurately representing local axonal orientation. This, coupled with the inferential nature of tractography algorithms, means that the technique may only provide an indirect and potentially incomplete picture of true fiber pathways (Rheault et al. 2020; Schilling et al. 2016, 2018).
- **Over-reliance on local orientation information**: Traditional tractography algorithms primarily rely on local orientation information derived from diffusion MRI. This limited information, without the integration of broader anatomical knowledge or other modalities, contributes to the inaccuracies observed in reconstructions (Bastiani et al. 2012; Daducci et al. 2016; Rheault et al. 2019; Schilling et al. 2022).
- **Limited validation in humans**: While validation studies in non-human primates and phantoms provide valuable insights, the direct validation of tractography in living human brains remains a significant challenge. Complementary post-mortem approaches such as Klingler post-mortem dissections (Akeret et al. 2022; Catani et al. 2012; Thiebaut de Schotten et al. 2011), myelin staining (Seehaus et al. 2015; Thiebaut de Schotten et al. 2011) can help decipher true connections from spurious reconstructions, but the absence of a definitive gold standard for human brain connectivity makes it difficult to assess the accuracy of tractography findings fully. Additionally, connectivity presents with a significant degree of variability between individuals, even at the macrostructural level (Catani et al. 2007; Croxson et al. 2018; Forkel et al. 2014; 2022) presents an additional level of complexity in the quest for the identification of the "true connectome". These approaches tackle structural connectivity across regions, an extension of the local tissue structures. For local structure, multiple post-mortem imaging techniques, such as polarized light imaging and polarized optical coherence tomography (OCT), offer high-resolution measurements to validate local models of fiber orientation.

Closing statement

No method is perfect, and the quest to unravel the mysteries of the human connectome is an ongoing endeavor. Despite its limitations, tractography continues to be an invaluable resource. While this technique has undoubtedly advanced our understanding of brain connectivity, the sources underscore the critical need for objective criticism, cautious interpretation, and continuous refinement. As we have seen, the inherent limitations of tractography, stemming from its inferential nature and the complex nature of the multiscale brain organization, can lead to inaccuracies and inconsistencies in reconstructions. Moving forward, a balanced anatomically-validated approach is crucial – one that recognizes the scale of interest and the strengths and weaknesses of tractography to answer neuroanatomical questions at the appropriate scale and ensure clinical use is reliable despite the limited availability of anatomical ground truth.

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Declarations

Competing interests The authors declare no competing interests.

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